REMARKS

Status of the Claims

Claims 1-16, 24-26 and 32 are pending in this application. Claim 33 has been canceled. No claims have been added. Claim 1 has been amended to define A as oxygen and to further define R^2 as including heteroarylalkyl having 1 to 9 carbon atoms and 1 to 4 heteroatoms. Applicants also amend claim 1 to define R_a and R_b as hydrogen or C_{1-6} alkyl groups. No new matter has been added by the above claim amendments.

Rejections under 35 USC 112, second paragraph

The Examiner rejects claims 1-16, 24-26, 32 and 33 as indefinite. Applicants traverse the rejection and respectfully request the withdrawal thereof. The following paragraph numbers correspond to the Examiner's paragraph numbers.

(iii) The Examiner states that "substituent" is indefinite because the specification states that it may "include, but is not limited to". Applicants amend the specification to delete the phrase "but not limited to." This amendment should overcome this rejection.

(iv) The Examiner states that "heteroaryl" is indefinite. Applicants amend the claims and submit that the heteroaryl may have 1-4 heteroatoms and may be 5-6 membered having 1 to 2 rings.

Moreover, heteroarylalkenyl is defined in the claims. As such, the rejection should be withdrawn.

(v) Applicants amend claim 1 to define R_a and R_b as hydrogen or C_{1-6} alkyl groups. Thus, the rejection should be withdrawn.

Rejections under 35 USC 112, first paragraph

The Examiner rejects claims 24-26 as not enabled for treating and ameliorating nerve degeneration diseases generally. Applicants traverse the rejection and respectfully request the withdrawal thereof.

Applicants submit that Alzheimer's disease and Parkinson's disease are caused by nerve degeneration. It is known that according to test data (i.e. *in vitro* or *in vivo*) nerve degeneration involves glutamic acid. It has been observed that tests of animal models having an occlusion or sprain in the cerebrum that an acute disease caused by nerve degeneration can be treated with a glutamic acid antagonist, in particular an AMPA receptor antagonist. The test data disclosed in the specification are supported by these known facts.

It is added that USP 5,962,457 to B. L. Chenard et al. was allowed with claims directed to a method of treating such a disease as Alzheimer's disease or Parkinson's disease merely with the disclosure about mechanism of AMPA antagonist. Moreover, the

test data disclosed in USP 5,962,457 is more simplistic than the data in the present specification.

In addition, Applicants submit that the list of references that follows further supports Applicants' position regarding enablement. Applicants will submit an Information Disclosure Statement in the near future for the Examiner's consideration.

1. Choi DW. Bench to bedside: The glutamate connection. Science 1992; 258:241-43.

2. Pellegrini-Giampietro DE. The G1uR2 (G1uR-B) hypothesis: Ca (2+)-permeable AMPA receptors in neurological disorders. Trends Neurosci 1997 Oct;20(10):464-70

3. Kohara N, et al,. Abnormal excitability of corticospinal pathway in patients with amyotrophic lateral sclerosis: a single motor unit study using transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1996; 101(1): 32-41.

4. Pioro EP. MR spectroscopy in amyotrophic lateral sclerosis/motor neuron disease. J Neurol Sci 1997;152 Suppl 1:S49-53.

5. Rothstein JD, et al. Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. Ann Neurol 1995; 38(1):73-84.

6. Lin CL, et al. Aberrant RNA processing in a neurodegenerative disease: the cause for absent EAAT2, a glutamate transporter, in amyotrophic lateral sclerosis; Neuron 1998; 20(3): 589-602.

7. Martin D, The neuroprotective agent riluzole inhibits release of glutamate and aspartate from slices of hippocampal area CA1. Eur J Pharmacol 1993; 250(3): 473-6 i 8. Hugon J. Riluzole and ALS therapy. Wien Med Wochenschr. 1996; 146(9-10): 185-7.

9. Selkeo DJ. Amyroid beta-Proptein and the genetics of Alzheimer's disease. J Biol Chem 1996; 271(31): 18295-98.

10.Shastry BS. Molecular genetics of familial Alzheimer disease. Am J Med Sci 1998; 315(4): 266-72.

11. Cummings JL, et al, Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment oppotumnities. Neurology 1998; 51 (1Supple1):S2-17; discussion S65-7.

12. Harris ME, et al,. Amyroid beta peptide (25-35) inhibits Na+-dependent glutamate uptake in rat hippocampal astrocyte cultures. J Neurochem 1996; 67(1): 277-86.

13. Klegeris A, McGeer PL. beta-amyroid protein enhances macrophage production of oxygen free radicals and glutamate. J Neurosci Res 1997; 49(2): 229-35.

14. Thorns V, et al,. Alteration in glutamate rceptor 2/3 subunits and amyroid precursor expression during the course of Alzheimer's disease and Lewy body variant. Acta Neuropathol 1997; 94: 529-48.

15. Rodrigues, M.C. et al., Subthalamic Nucleus-mediated exicitotoxicity in Parkinson's disease: A atrget for Neuroprotection. Ann Neurol 1998; 44 (Suppl 1): S175-5188.

16. Piallat, B Benazzouz A, Benabid AL. Subthalamic nucleus lesion in rats preventa dopaminer (gicnigral neuron degeneration after striatal 6-OHDA injection: behavioral and immunohistochemical studies. Eur J Neurosci 1996; 8(7): 1408-14.

17. Loschmann PA, et al. Synergism of the AMPA-antagonist NBQX and the NMDA-antagonist CPP with L-dopa in models of Parkinson's disease. J Neural Transm Park Dis Dement Sec 1991; 3 (3): 203-13.

18 . Klockgether T. et al., The AMPA receptor antagonist NBQX has antiparkinsonian effect in monoamine-depleted rats and MPTP-treated monkeys. Ann Neurol 1991; 30(5): 717-23.

19. Loschmann PA, Kunow M, Wachtel H. Synergiam of NBQX with dopamine agonistsin the 6-OHDA rat model of Parkinson's disease. J Neural Transm Suppl 1992; 38:55-64.

Applicants further submit that similar to cerebrovascular disorder acute stage, the case where the stress by the increase of

stimulus of glutamic acid or glutamate receptor agonist serves as a trigger and causes neuropathy is reported in reference number 1.

Many AMPA receptors do not have calcium ion permeability. However, when the expression of GluR2 receptor regulating the calcium ion permeability is reduced, intracellular $Ca2^{+}$ ion is increased. These two factors or a mixed factor of them are considered to cause nerve death as described in references 1 and 2. Accordingly, the preventive effect of the disease and the therapeutic effect of suppressing the progress of clinical conditions after the onset of a symptom are expected by using an AMPA receptor antagonist for preventing or treating the disease.

ALS is a chronic nerve degeneration disease which involves glutamic acid. ALS is a nerve degeneration disease in which degeneration is caused in the motor nerves of spinal chord and cerebrum. As reported in an ALS patient, the excitability of corticospinal tract neurons is in a hyper state. See reference 3. It is also reported in reference 4 that the glutamic acid to glutamine level is extremely high in such a patient. Since abnormality of glutamate transporter, which is the excreting mechanism of extracellular glutamic acid, is observed in ALS patients, the relationship between glutamic acid and ALS is considered to be extremely close. See references 5 and 6. Further, currently, Rilzole (reference 7) which is an inhibitor of glutamate

release is recognized as the only efficacious medicament for treating ALS (reference 8). This is the reason for using glutamate receptor antagonists for treating or preventing ALS.

Alzheimer's disease is a disease in which amyloid β protein (Aβ) relates to the clinical conditions (references 9,10 & 11), and it is known that uptake of glutamic acid extracellularly is inhibited by the action of Aβ on astroglia having a function of maintaining a particular environment in the brain, such as uptake of neurotransmitters. See reference 12. Further, it is known that the release of glutamic acid is caused by action of the amyloid β protein (Aβ) on a macrophage. See reference 13.

It is further considered that the concentration of the glutamic acid existing in intercellular space in the brain is elevated due to these mechanisms, and that stimuli via a glutamate receptor is excessively burdensome on neurons. Further, it is reported that, in a patient's brain, GluR2 or G1uR3, which is a subunit of AMPA receptor is reduced even though NMDA receptor similarly expressed on neurons is not reduced. See reference 14. From the above, it is considered that excessive activation of AMPA receptor and increase of calcium ion inflow are caused due to the elevation of the concentration of glutamic acid, and that nerve death due to improper regulation of the $Ca2^{+}$ permeability of AMPA receptor is important in the onset and progress of Alzheimer's

disease. Accordingly, the preventive effect of the disease and the therapeutic effect of suppressing the progress of clinical conditions after the onset of symptom are expected, by using AMPA receptor antagonist for preventing or treating the disease.

Parkinson's disease is a disease in which dopamine neuron in the nigrostriate system in the brain is selectively and progressively disordered. In this disease, the nerve releasing glutamic acid as the neurotransmitter projects to nigrostriatal dopaminergic nerve from nucleus subthalamicus. It is suggested that excitatory of the nucleus subthalamicus nerve is accelerated by Parkinson's disease, whereby hyperexcitability of the dopamine neuron by glutamic acid is caused and finally resulting in nerve death of the dopamine neuron. See reference 15.

Actually, it is suggested that by suppressing excitatory neurotransmission from nucleus subthalamicus by destruction of the nucleus subthalamicus, dopamine neuron can be protected in 6-OHDA nigrostriatal destructed animals, which is a Parkinson's disease model. See reference 16. Further, it is considered that AMPA receptor antagonist is also involved in Parkinson syndrome. See references 17,18 & 19. Besides the preventive effect of the disease and therapeutic effect of suppressing the progress of the clinical conditions as a nerve-protecting agent, the agent is expected to be useful for symptomatic treatment as well.

As described above, there is an abundance of data showing nerve hyperexcitability due to the increase in extracellular glutamic acid is occurring in various nerve degeneration diseases. It is believed that the degeneration of AMPA receptor causes nerve degeneration. Actually, among various nerve-protecting agents, only a suppressor of glutamic acid release exhibited an effect for ALS, which is the most severe nerve degeneration disease.

For the foregoing reasons, Applicants submit that the present invention is enabled and the rejection should be withdrawn.

Rejection under 35 USC 103(a)

The Examiner rejects claim 1 as obvious over Dekeyser et al. USP 4,670,555. Applicants traverse the rejection and respectfully request the withdrawal thereof.

The Examiner states that the three carbon chloroalkyl in R^{11} is made obvious by the two carbon chloroalkyl or any two carbon haloalkyl.

Applicants submit that the present invention is not made obvious over the cited reference. Applicants submit comparative data in a Declaration under 37 CFR 1.132 prepared by Mr. Hanada demonstrating that the compound of Dekeyser '555 does not suggest the compounds of the present invention.

Mr. Hanada tested sample numbers 74,125, 163, 187 and 188 of the present invention against sample numbers 44, 45, 48, 68, 114 and 132 of Dekeyser '555. The results of the testing are reported in attached charts. It is apparent from the results that the present invention is unexpectedly superior over Dekeyser '555 in inhibitory action of AMPA-inducing inflow of calcium into nerve cells.

As such, Applicants submit that the present invention is not made obvious over Dekeyser '555 as the present invention exhibits unexpectedly superior results as demonstrated in the attached Declaration under 37 CFR 1.132 of Mr. Hanada. Thus, Applicants respectfully request that the rejection be withdrawn.

Conclusion

As Applicants have addressed and overcome all rejections in the Office Action, Applicants respectfully request that the rejections be withdrawn and that the claims be allowed.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kecia Reynolds (Reg. No. 47,021) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment(s): Declaration under 37 C.F.R. 1.132